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(54) **Sustained-release formulation containing an amin acid polymer with a lower alkyl (C1-C4) polar solvent.**

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Description

This invention relates generally to a novel sustained-release formulation which gradually releas s a medicinal agent therefrom. In a specific embodiment th invention pertains to a formulation for slowly dispensing a drug in the eye.

It is basically known in the art that medicinally active substances may be dissolved in the aqueous constituent of hydrogels to gradually release such substances over an extended period. For example, U.S. Patent No. 3,220,960 describes utilizing a hydrogel in the eye as a carrier for time release medicaments such as boric acid or penicillin. Similarly, U.S. Patent Nos. 3,551,556; 3,641,237; 4,003,991; and 4,271,143 disclose slowly releasing an active ingredient from an insoluble, cross-linked hydrogel in one form or another. Several compositions illustrated in the latter two patents are comprised of viscous, long-acting gel preparations where the prolongation of biological activity of the ophthalmic drug results from a slow erosion of the gel surface. The formulation in U.S. Patent No. 3,551,556 shows granular non-ionogenic, neutral, insoluble hydrogels which are useful for oral or intramuscular application. Further, many patents are directed to ocular insert devices which prolong the effect of a drug incorporated within the device. Such patents include U.S. Patent Nos. 3,811,444; 3,826,258; and 3,786,812.

These prior carriers of medicaments present certain difficulties during their use, particularly with ophthalmic drugs The predominant complaint with long-acting gel formulations is blurred vision. Another difficulty is the inability to wear corrective contact lenses when a viscous material will be instilled and remain in the eye over an extended period of time. The ocular insert devices also present certain disadvantages with their use. When inserted into the conjunctival sac, such devices create a strong foreign body sensation and discomfort for the patient. The insert devices must be changed weekly. Additionally, the devices tend to fall out of the eye easily and cannot be used further by the patient since they are not capable of being sterilized.

Similarly, conventional contact lenses containing a sustained-release medicine carrier have drawbacks in practice. They have been found to possess inadequately controlled or prolonged release characteristics making the conventional lenses unsuitable and impractical as sustained-release devices. The concept of soaking a high water content material in a drug solution has been used with conventional hydroxyethyl methacrylate based contact lenses, for example, a polymerized hydrophilic monomer or soft contact lens such as Soflens® manufactured by Bausch & Lomb. See Ruben et al., British J. Ophthal., 59:455 (1975). In practice, Soflens®, however, provides an inefficient system and is an unsuitable device for prolonged release. Experimental studies have shown that Soflens® will release 100% of pilocarpine hydrochloride in buffered saline and distilled water in merely 1 1/2 and 2 1/2 hours, respectively.

The object of the present invention is to provide a sustained-release polymeric hydrogel dosage form that is useful for topical, systemic or transdermal administration of medicinal agents, particularly ophthalmic drugs, and which is moldable to any desired shape, with moldability to the shape of the cornea of the eye being of major interest.

Thus, the present invention provides a sustained-release polymeric hydrogel dosage form useful for topical, systemic or transdermal administration of a medicinal agent comprising (1) a cross-linked, hydrophilic copolymer containing units derived from (a) an olefinically unsaturated hydrophilic monomer and (b) an amino acid monomer, and (2) a medicinal agent, wherein said medicinal agent has been incorporated by adding it to the copolymer solution obtained following initial polymerisation of said monomers in a (C_1-C_4) alkyl polar solvent but prior to cross-linking of the copolymer, whereby said medicinal agent is retained in the copolymer matrix but is slowly releasable from said copolymer upon tissue contact.

A specific embodiment of the invention is an ophthalmic dosage form that can concurrently correct vision and release medication to the eye, i.e. a contact lens with both cosmetic and therapeutic value.

In accordance with the present invention, the hydrogel formulation employed as a sustained-release dosage form comprises one or more cross-linked hydrophilic copolymers derived from an olefinically unsaturated hydrophilic monomer and an amino acid monomer.

The hydrophilic monomer used in the polymer of this invention can be present in varying amounts, desirably from 50% to 90% w/w and, more preferably, from 74% to 84% w/w of the total monomers present in the polymerization mixture. These monomers include, for example, the hydroxyalkyl esters and amides, both N-substituted and unsubstituted, of alpha-,beta-unsaturated carboxylic acids, N-vinyl lactams and 2-acrylamido-2-methylpropan sulfonic acid. Useful alpha-,beta-unsaturated acids include acrylic acid, crotonic acid, methacrylic acid, itaconic acid, maleic acid, maleic anhydrid and fumaric acid. Th polyfunctional alcohols which form th hydroxyalkyl esters can include, for example, glycol, glycerol, propylene glycol, trimethylen glycol and other polyhydric alkanols, dialkylene glycols of 2 to 12 carbon atoms and polyalkylen glycols. Polyalkylen glycols are exemplified by triethylene glycol, tetra thylen

glycol, pentaethylen glycol and hexaethyl ne glycol. The preferred hydrophilic monomers are th hydroxyalkyl esters, specifically hydroxyethyl m thacrylat (HEMA).

Us ful amides of th foregoing acids include diacetone acrylamide and N-mono-substituted diaceton acrylamide. Also us ful ar the amin s of th foregoing acids such as mono- or di-alkylamino substituents.

A nitrogen containing monomer which may be used as the olefinically unsaturated hydrophilic monomer in the preparation of the copolymers used in this invention is conveniently referred to as N-vinyl lactam, which term includes (a) N-vinyl lactams per se and (b) other heterocyclic N-vinyl monomers. Illustrative of the N-vinyl lactams that can be employed in this invention are N-vinyl-2-pyrrolidinone, N-(1-methyl vinyl) pyrrolidinone, N-vinyl-2-piperidone and N-vinyl-2-caprolactam, which may be substituted in the lactam ring by one or more lower alkyl groups such as methyl, ethyl or propyl, e.g. N-vinyl-5-methyl pyrrolidinone, N-vinyl-3,3-dimethyl pyrrolidinone, N-vinyl-5-ethyl pyrrolidinone and N-vinyl-6-methyl piperidone. Illustrative of the other heterocyclic N-vinyl monomers which can be used in preparing the copolymers used in this invention are N-vinyl imidazole, N-vinyl succinimide, N-vinyl diglycolylimide, N-vinyl glutarimide, N-vinyl-3-morpholinone and N-vinyl-5-methyl-3-morpholinone. Such lactams may be employed alone or in admixture with other lactam monomers.

The second monomeric component forming the copolymer used in this invention is an alpha,beta-unsaturated carbonyl-modified or unmodified amino acid monomer or monomers. This component also can be present in varying amounts but desirably is present in an amount from 5% to 27% w/w and more preferably constitutes about 6% w/w of the total monomers present in the polymerization mixture. The modified or unmodified amino acid monomers are hydrophilic compounds which contribute significantly to the swelling of the polymer in water and permit higher oxygen diffusion.

The alpha-,beta-unsaturated carbonyl modifier for the modified amino acids used in this invention may be, for example an aliphatic mono- or di-carboxylic acid or an aromatic tri- or tetra-carboxylic acid, for instance acrylic acid, crotonic acid, methacrylic acid, maleic acid, fumaric acid, itaconic acid and their functional derivatives, i.e. acid chlorides, anhydrides, amides and esters. The more preferred modifiers are methacrylic acid and methacroyl chloride.

An amino acid is an organic acid whose molecule contains both a carboxyl group (COOH) and an amino group (NH_2) coupled with an alkyl, cycloalkyl, aryl or heterocyclic structure, the alkyl, cycloalkyl or heterocyclic structure being free of olefinic unsaturation. The alpha,beta-carbonyl substituent can be attached to either the amino group or the hydroxy group of the amino acid, depending on the structure of the amino acid. Additionally, the carbonyl substituent can attach to other reactive groups, if present, in the amino acid, e.g. thiol (SH) or phenolic hydroxyl.

Amino acids useful in the preparation of the modified acids used in this invention include, but are not limited to beta-alanine, gamma-aminobutyric acid, omega-aminocaproic acid, omega-aminododecanoic acid, beta-cycanoalanine, epsilon-methylhistidine, canavanine, djenkolic acid, 1-azaserine, gamma- methylene glutamic acid, N-methyltyrosine, glycine, alanine, serine, cystine, cysteine, lanthionine, phenylalanine, tyrosine, diiodotyrosine, tryptophan, histidine, aminobutyric acid, methionine, valine, norvaline, leucine, isoleucine, norleucine, arginine, ornithine, lysine, aspartic acid, glutamic acid, threonine, hydroxyglutamic acid, proline, hydroxyproline, asparagine, glutamine, desmosine, isodesmosine and 5-hydroxylysine. Preferred amino acids are glycine, glutamic acid, desmosine and isodesmosine.

It should be understood that other, though perhaps less common, amino acids occurring in nature or prepared synthetically, including those shown in the examples which follow, are within the scope of this invention. Reactive sites on the amino acids can be partially blocked by saturated nonpolymerizable substituents provided that one reactive site is substituted by the alpha-, beta-carbonyl substituent.

The polymers used in this invention may be cross-linked by all types of cross-linking compounds used in the prior art, see for instance, U.S. Patent Nos. 3,822,089; 4,152,508; and 4,440,919. The cross-linking agent can be employed in varying amounts and desirably in an amount from 3 to 30 parts by weight of the total monomers present. Examples of suitable cross-linking agents include polyfunctional derivatives of the previously enumerated alpha-, beta-unsaturated acids, e.g., acrylic acid, methacrylic acid, crotonic acid, itaconic acid, maleic acid, fumaric acid, acrylamide, methacrylamide, and multi-vinyl substituted benzenes. More particularly these cross-linking agents include the following: ethylene glycol diacrylate or dimethacrylate, diethylene glycol diacrylate or dimethacrylate, triethylene glycol diacrylate or dimethacrylate, tetraethylene glycol diacrylate or dimethacrylate, polyethylene glycol diacrylate or dimethacrylate, trimethylolpropane triacrylate or trimethacrylate, bisphenol A diacrylate or dimethacrylate, ethoxylat d bisph nol A diacrylat or dimethacrylat , pentaerythritol tri- and t tra-acrylate or methacrylate, tetramethyl n diacrylate or dimethacrylate, m thylene bisacrylamide or methacrylamid , dim thylen bisacrylamide or methacrylamid , N,N'-dihydroxy thylene bisacrylamide or m thacrylamid , hexamethylen bisacrylamide or methacrylamid , d camethyl ne bisacrylamide or methacrylamide, divinyl benz n , vinyl

methacrylate and allyl methacrylate. A preferred cross-linking agent is allyl methacrylate.

Still other useful cross-linking agents include 1,3-bis(4-methacryloyl oxyalkyl) t tra disiloxan and similar poly (organo-siloxane) monomers as s t forth in U.S. Patent No. 4,153,641. Another group of useful cross-linking agents are th resonance fr e di(alkylene tertiary amine) cyclic compounds, e.g. N,N'-divinyl ethylene urea, as disclosed in U.S. Patent No. 4,436,887. Yet another group are di- or polyvinyl ethers of di- or polyvalent alcohols such as ethylene glycol divinyl ether.

It is an important feature of the instant invention that the monomers are polymerized in a lower alkyl (C_1-C_4), polar solvent, preferably volatile, demonstrating high water solubility parameters, for example a lower alkyl (C_1-C_4) alcohol, or a ketone, for controlling the viscosity of the polymer. Suitable solvents may also include mixtures of different ketones in any proportions and mixtures of a lower alkyl (C_1-C_4) alcohol and water in any proportion. Examples of particularly suitable solvents are methanol, ethanol, propanol, butanol, isopropanol, acetone, methyl ethyl ketone and hydroxyacetone. Typically, equal parts of solvent monomers are used in the preparation of the polymers. However, different amounts of the solvent may be used with the monomers though generally less conveniently. When the process of this invention is followed, the residue of the solvent remains in the formulation in varying amounts depending upon reaction conditions such as time and temperature. Preferably trace amounts of the residue are present for ophthalmic use and higher amounts are present for transdermal use.

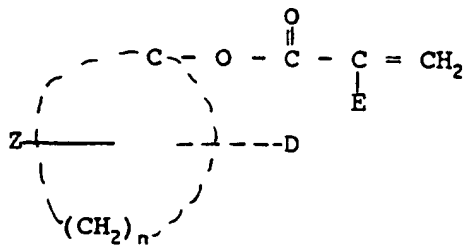
Optionally, a chain regulator or chain transfer agent may be added if a particular monomer-solvent combination requires it. For example, certain combinations containing solvents such as butanol may require large quantities of butanol which may not be desirable in the product. If a chain regulator is added, a smaller amount of butanol may be used.

The term "chain regulator" refers to any chemical that controls the molecular weight of the polymer during polymerization. A chain regulator may be optionally employed in varying amounts and desirably in an amount from 0.01% w/w to 0.5% w/w. Examples of chain regulators include dodecanethiol, isopropyl mercaptan and decanethiol. A particularly preferred chain regulator is dodecanethiol.

For some applications the copolymerizates formed from the above-described hydrophilic monomer(s), modified or unmodified amino acid monomer(s), cross-linking agent(s), a lower alkyl (C_1-C_4) alcohol and optional chain regulator, may lack the desired physical handling properties. In such circumstances it may be desirable to incorporate one or more hydrophobic monomers in the reaction mixture in varying amounts, preferably from 8% to 20% w/w of the total monomers present. More preferably the hydrophobic monomer would be present in an amount of about 10% w/w of the total monomers present. Among other things, the hydrophobic monomers can be useful as modulus modifiers.

The modulus modifier may be, for example, a cycloalkyl ester, tertiarybutyl styrene and a polycyclic acrylate or methacrylate, as well as mixtures thereof. More particularly the polycyclic modifiers may be isobornyl acrylate, isobornyl methacrylate, dicyclopentanedienyl acrylate, dicyclopentanedienyl methacrylate, adamantyl acrylate, adamantyl methacrylate, isopinocamphyl acrylate and isopinocamphyl methacrylate, and mixtures thereof. The cycloalkyl ester modifiers may be of formula I below. Illustrative of these cycloalkyl modifiers are menthyl methacrylate, menthyl acrylate, tertiarybutyl cyclohexyl methacrylate, isohexyl cyclopentyl acrylate and methylisopentylcyclooctylacrylate.

(I)



wherein:

D is branched or normal alkyl of 3 to 6 carbon atoms

E is H or CH_3

Z is H or CH_3, and

n is an integer from 3 to 8.

In addition to hydrophobic monomers which can serve as modulus modifiers, other w ll known hydrophobic monomers may be used in the formulation of the copolymers used in this invention to further

tailor the properties to th particular application. Thus, the hydrophobic monomers used in this invention can include monomers which contain at l ast on silicon or fluorine atom as a part of its composition. Such hydrophobic monomers include alkyl, cyclo-alkyl and aryl acrylates and methacrylates as well as mono- or disubstituted itaconates, styrene and its d rivativ s, acrylonitrile, vinyl est rs such as vinyl acetate or vinyl pentacetyl gluconate, vinyl ethers such as vinyl butyl ether, allyl esters such as allyl acetate, propionate or butyrate, fluorine containing monomers such as octafluoropentyl methacrylate and silicon containing monomers, e.g. 1,1,1-tris (trimethoxysiloxy)-3-methacryloxy-propylsilane or heptamethyltrisiloxanyl ethyl acrylate.

The monomeric mixtures, comprising the hydrophilic monomer(s), the modified or unmodified amino acid monomer(s), the optional hydrophobic monomer(s), the cross-linking agent, the lower alkyl (C_1-C_4) alcohol and the optional chain regulator are generally clear, colorless liquids of varying viscosity. These monomer mixtures are initially polymerized but not cross-linked for example by using ultraviolet light at room temperature. According to another important feature of this invention, the medicinal agent is added to this linear, polymerized polymer before it is cross-linked. Cross-linking is achieved, for example, by ultraviolet light and/or heat. Before cross-linking takes place, the linear polymer is characterized by being soluble in methanol and isopropanol. After cross-linking, an insoluble polymer is formed.

As catalysts which may be used for carrying out the polymerization, there may be employed a free radical catalyst (initiator) in varying amounts and typically in the range of 0.05% to 3% w/w of the polymerizable monomer mixture. The preferred amount of catalyst is 0.1% is 2.5% w/w of the total monomers present. Usually, the catalyst is added initially to the monomers and then the polymerization procedure is completed. Free radical type initiators suitable for this invention include peroxides, azo compounds, oxidation-reduction systems and similar initiators described in the literature. Typical catalysts include benzoin methyl ether, tertiary-butyl-peroctoate, benzoyl peroxide, isopropyl percarbonate, methyl ethyl ketone peroxide, cumene hydroperoxide, dicumyl peroxide, bis(isopropyl) peroxydicarbonate, 2,2'-azobis [isobutyronitrile], acetyl peroxide, lauroyl peroxide, decanoyl peroxide, 2,2'-azobis[2,4-dimethylvaleronitrile], phthalic peroxide, diethoxyacetophenone and tertiary-butyl peroxypivalate. Thermal catalysts, visible light or irradiation, e.g., by ultraviolet light or gamma rays, also can be employed to catalyze the polymerization. Polymerization can be done at 20° to 150°C, usually 40° to 90°C. Prior to adding the medicament and cross-linking the polymer, the prepolymerization of the monomer mix is preferably achieved at room temperature, usually 20° to 28°C, to create a linear, polymerized polymer. Cross-linking is preferably achieved by using a suitable amount of heat, typically 65° to 75°C. The choice of catalyst obviously depends upon the temperature desired for the reaction.

Water soluble diluents may, if desired, be used to modify the physical properties of the polymers. More particularly, the diluents may be advantageous in improving machinability and swell characteristics of the polymer. Typically, the amount of diluent will be less than 50 weight percent of the total monomers employed and preferably not more than 30 weight percent. In a particular polymer system, the limiting amount of diluent is the solubility of the diluent in the monomer system. Thus, there should be no phase separation between diluent and starting monomer mixture. Additionally, excessive amounts of diluent will result in collapse of the cell structure of the finished biomedical devices when the device is hydrated, i.e., replacement of diluent by water. The maximum amount of diluent is readily ascertained by swelling the diluent free polymer in the proposed diluent and measuring the degree of swell. Comparable results are obtained when using solvent soluble diluents wherein the solvent does not affect the lens polymer. Suitable diluents include ethylene glycol, glycerin, liquid polyethylene glycols, butanol, butanol/water mixtures, ethylene oxide/propylene oxide block copolymers having a molecular weight from 1,000 to 5,000, linear poly(vinyl pyrrolidinone) having a molecular weight from 500 to 10,000, low molecular weight linear poly-(hydroxyethyl methacrylate), glycol esters of lactic acid, formamide, dimethyl formamide and dimethyl sulfoxide. In the finished biomedical device, it will be necessary to replace any diluent with an aqueous solution. With respect to contact lenses, the final water content of the polymeric composition typically ranges from 25% to 70% w/w. The contact lens should, of course, contain a physiological saline solution as the aqueous medium.

Using methods well known in the art, the sustained-release formulation of this invention can be formed into a variety of shapes depending upon the end use and desired results to be obtained therefrom. For ophthalmic purposes, the polymeric hydrogel could have any form to maintain direct contact with the eye. It is not necessary to cover the entire cornea if the dosage form is merely used to instil a continuous flow of an ophthalmic drug in the ye. If the hydrogel will also be used to correct vision, then it may be desirable to cast the polymer on an optical mold.

By way of exampl , the mixtur of hydrophilic monomer(s), modified or unmodified amino acid monomer(s), cross-linking ag nt, free radical initiator and optional hydrophobic monomer(s) described

above is prepared. If desirable, a chain regulator is added to this mixture. Then a lower alkyl (C_1-C_4) alcohol is added. A two-stage proc ss is carried out by forming a linear, polymerized polymer by ultraviolet light at room temperature and cross-linking th polymer by subsequent application of heat together with ultraviolet light if needed. Between these two stages the medicinal agent is added whereby th medicinal agent is retained by the polymeric matrix of the resulting polymeric hydrogel but, upon tissue contact, is gradually released into the tissue. Thus, the medicinal agent is added directly into the linear, uncross-linked polymer and becomes intimately mixed in the polymeric matrix rather than remaining as particulate matter. Subsequent cross-linking prevents copolymerization of the medicinal agent with the polymer allowing for greater recovery of the medicinal agent upon tissue contact. The drug will thus release slowly into the tissue for local or systemic effect over prolonged time intervals at lower concentrations, thereby helping to eliminate or reduce side effects.

The amount of the medicinal agent used in the preparation of the dosage forms will vary depending upon the physicochemical properties of the selected medicinal agent and the therapeutic effect desired to be achieved. Typically, the medicinal agent is added on a equivalency basis, that is, an equivalent for equivalent basis of medicinal agent to the linear, polymerized polymer. Although a stoichiometric number of equivalents of medicinal agent and the linear, polymerized polymer is preferred, other amounts can also be used. As an example of pilocarpine hydrochloride, varying concentrations of the compound may be employed, desirably an amount from 5% to 15% w/w, of pilocarpine hydrochloride to the weight of the linear polymer, and preferably 9.1% w/w, for incorporation in the dosage form.

The polymeric composition of the instant invention provides appreciable time release of the medicament. The release rate of a medicinal agent from the polymeric matrix varies with cross-linking density and type of polymer barrier system. Additionally, the release rate depends upon the viscosity of the linear, uncross-linked polymer initially formed, which is controlled by the addition of the (C_1-C_4) alkyl polar solvent such as lower alkyl (C_1-C_4) alcohol.

To quantify the release rate of a sustained release polymeric hydrogel dosage of this invention formed into a lens, lenses with and without medicament can be placed in a known quantity of release media (distilled water or buffered saline) and stirred with a magnetic stirrer. At various times the lenses can be transferred to fresh media and the absorbance of the previous media can be determined by ultraviolet spectroscopy. The absorbance of the media containing drugged lenses is reduced by the absorbance of the media containing undrugged lenses. Use of a calibration curve relating absorbance to concentration allows for a determination of the concentration of the medicament. The calibration curve is developed by measuring the absorbance of known concentrations of the drug in the release media. As the concentrations (µg/ml) of the medicament and the volume (ml) of release media are known, the amount of the released medicament can be calculated (µg). This value divided by the time of exposure to the media gives the release rate in µg/hr which is plotted against time.

The copolymers employed in this invention being soft yet resilient and hard to tear are well suited for preparing biomedical devices, including contact lenses, which have the ability to release medications from the polymeric matrix over a prolonged period of time. It is well known that the wearer of soft contact lenses will have an unavoidable amount of handling of the lenses. Part of the cleaning and rinsing procedure is to rub each lens and tearing has been a concern in prior art lenses. The polymers and copolymers used in the present invention can have a tear initiation strength (ASTM D-1938) of up to 5 g/mm of thickness. Contact lenses made from the copolymers utilized in the instant invention are oxygen permeable. A critical oxygen tension and flux under a lens should be about 10 mm Hg and 2 $\mu l/cm^2 hr$.) respectively below which corneal swelling occurs, see Polse and Decker, Investigative Ophthalmology and Visual Science, 18:188 (1979). In order to meet these requirements, the lens material must have adequate oxygen permeability. The preferred contact lenses in accordance with this invention have an oxygen permeability of at least about 24 x 10^{-11} $cm^3 cm/(sec.cm^{2 mmHg})$, are hyrolytically stable, biologically inert and transparent. In comparison, the well-known contact lens polymer polyhydroxyethyl methacrylate has an oxygen permeability value of about one-third of the preferred copolymers used in this invention.

Additionally, these lenses are hydrolytically stable, meaning that when the contact lenses are placed into an aqueous solution (e.g. on the eye) or during the disinfecting step (i.e. water plus heat), the lenses will not change in chemical composition. That is, they will not hydrolyze. On heating in boiling water for 120 hours, the typical polymer of this invention experiences a water content loss of 3% or less. The most preferred lens s/polym rs us ful in this invention hav a stable water content that undergoes less than 1% chang . Thus, copolymers disclosed herein can be boiled and/or autoclaved in water without being damaged whereby st rilization may be achieved. In addition, sterilization can be achieved by gamma-irradiation, ultraviolet light irradiation and ethylen oxide exposure.

Oth r biom dical devices may be formed from the disclosed copolym rs and used to administer medications to mammals wh re an article compatible with living tissue or with the mucous membranes is desired.

Thus the instant invention provides a nov l sustained-release polymeric hydrog l dosage form useful for topical, systemic or transdermal administration of a medicinal agent comprising the above-described polymeric matrix in association with a therapeutically effective amount of the medicinal agent. When prepared according to the teachings of this invention, the polymeric matrix permits the active ingredient to be subsequently released at a gradual, carefully controlled rate prolonging the time release period. In contrast to normal disintegration time, the sustained-release administration of medicaments enhances therapeutic effectiveness and decreases many undesirable side effects by maintaining constant tissue and blood levels.

The polymeric hydrogel dosage form can be used in preparing biomedical devices that upon surgical implant will provide sustained-release activity of the active ingredient. Depending on the location of the implant, the therapeutic effect may be local or systemic. The dosage form can also provide for the oral or topical (i.e., localized activity on the skin) controlled-release administration of medicaments. Additionally, the dosage form can be utilized for the transdermal controlled-release administration of medicaments, i.e., the device is retained in contact with the skin for transdermal absorption of the medicament into the blood for systemic effect. Contact with the skin may be achieved by any means well-known in the art such as by incorporating an adhesive in or on the device or adhering the device within or onto a bandage-type article.

Further, the dosage form can be useful for the ophthalmic route of administering medicinal agents for either local or systemic therapeutic effect. For ophthalmic administration of a medicament to produce local or systemic activity, the polymeric composition can be molded into any convenient shape for eye contact. If correcting vision is not necessary, the dosage form does not have to cover the entire cornea. Alternatively, the polymeric hydrogel can be shaped into contact lenses on optical molds if it is desirable to correct vision in addition to administering ophthalmic medicaments.

The length of time for contacting the polymeric hydrogel device containing a medicament with a tissue of a mammal depends upon the individual circumstances of each case. A sufficient amount of time to achieve a constant therapeutic effect varies in accordance with the optimum therapeutic effect desired. The duration of therapy is, of course, contingent upon the disease or medical problem being treated or palliated. Likewise, the therapeutically effective amount of the specific medicinal agent is determined by therapy requirements and the biophysical properties of the active compound. For example, with respect to contact lenses, the invention contemplates daily wear or extended wear, typically, up to a month. To treat an eye infection, it would be desirable to maintain the contact lens containing an antibiotic or an antiviral agent on the eye for one to two weeks. On the other hand, to treat glaucoma, it would be desirable to wear the lens containing an agent for reducing intraocular pressure for the maximum time that extended wear contact lenses can remain in the eye.

The term "dosage form" refers to physically discrete units suitable as unitary dosage for mammals, each unit containing a predetermined quantity of active component calculated to produce the desired therapeutic effect.

The term "a medicinal agent" means a substance useful in treating or ameliorating a disease or medical condition. For purposes of this invention, "a medicinal agent" refers to drugs which would have the capacity to be bound to the amino acid moiety of the polymeric hydrogel. That is, any drug or its salt with polar characteristics that interacts with the amino acid moiety in a favorable way can be used in the present invention. Examples of medicinal agents include antibiotics, antivirals, anti-inflammatories, steroids, peptides, polypeptides, cardiotonics, antihypertensives, antiallergics, alpha-and beta-adrenergic blocking agents, anticataract agents, ophthalmic medicaments, ophthalmic lubricating agents, and opthalmic topical or regional anesthetic agents. The ophthalmic medicaments or other medicinal agents encompass such drugs as pilocarpine, idoxuridine, carbachol, bethanechol, timolol, tetracycline, epinephrine, phenylephrine, eserine, phospholine, demecarium, cyclopentolate, homatropine, scopolamine, nitroglycerin, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, penicillin, erythromycin, sulfacetamide, polymyxin B, tobramycin, isofluorophate, fluoromethalone, dexamethasone, hydrocortisone, fluorocinolone, medrysone, prednisolone, methyl prednisolone, betamethasone, triamcinolone, interferon, cromolyn and all-trans-retinoic acid (Vitamin A), and the nontoxic, pharmaceutically acceptable salts thereof. The category of ophthalmic lubricating agents refers to those agents capable of inducing natural lacrimation or creating artificial lacrimation and includes, for exampl , polyvinyl alcohol, cellulose polym rs such as hydroxypropyl methyl cellulose, a polylactam such as polyvinylpyrrolidinone and other tear inducers or substitut s. The topical or regional anesthetic agents, which may b useful during ophthalmic surgery or oth r ophthalmic procedur s, include lidocaine, cocaine, benoxinate, dibucain ,

proparacaine, tetracaine, etidocain , procaine, hexylcaine, bupivacaine, mepivacaine, prilocain and chloroprocaine.

The term "pharmac utically acceptable salt" refers to those salts of the parent compound which do not significantly or adversely affect the pharmaceutical properti s (.g., toxicity and efficacy,) of the parent compound. The salts of the present invention which are pharmaceutically acceptable include, for example, chloride, iodide, bromide, hydrochloride, acetate, nitrate, stearate, phosphate and sulfate. It is desirable to use the appropriate salt form of the active ingredient which would increase the water solubility or polar characteristics of the base compound.

In addition to human medical uses, the above described polymeric hydrogel may be found useful with veterinary products for the treatment of animals.

The invention is illustrated by the following Examples in which all parts and percents are on a weight basis and all temperatures are expressed in degrees Celsius unless otherwise specified.

Except for the crosslinking step, which was done at 70 °C, these examples were conducted at room temperature (about 23 °C to about 28 °C), and at atmospheric pressure.

Example 1

Preparation of a Hydrogel Polymer Containing Pilocarpine Hydrochloride

A mixture is prepared by combining 74.5 g of 2-hydroxyethyl methacrylate (HEMA) containing 0.12% of ethylene glycol dimethacrylate (EGDMA), 10 g of isobornyl methacrylate (IBOMA), 6 g of methacroyl glycine (MG), 2.5 g of benzoin methyl ether (BME) and 0.1 g of 2, 2'-azobis] isobutyronitrile]. To the mixture is added 5 g of allyl methacrylate. To 5 g of the mixture is added 5 g of methanol. This mixture is then purged with nitrogen and polymerization is performed with stirring under ultraviolet light (UV) at room temperature for 2 hours. When a honey-like consistency develops, 0.205 g of pilocarpine hydrochloride is added to 4 g of the linear polymer forming a clear solution. The solution is cross-linked with a subsequent exposure to UV for 30 minutes at room temperature and then to UV for 30 minutes at 70 °C.

Example 2

Preparation of a Hydrogel Polymer Containing Pilocarpine Hydrochloride

The procedure of Example 1 is repeated to prepare the hydrogel poly mer with the additional step of adding 0.01 g of dodecanethiol after the allyl methacrylate is added to the mixture.

Example 3

Preparation of a Hydrogel Polymer Containing Pilocarpine Hydrochloride

The procedure of Example 1 is repeated to prepare the hydrogel polymer with the additional step of adding 0.02 g of dodecanethiol after the allyl methacrylate is added to the mixture.

Example 4

Preparation of a Hydrogel Polymer Containing Pilocarpine Hydrochloride

The procedure of Example 1 is repeated to prepare the hydrogel polymer with the additional step of adding 0.25 g of dodecanethiol after the allyl methacrylate is added to the mixture.

Example 5

Preparation of a Hydrogel Polymer Containing Pilocarpine Hydrochloride

The procedur of Example 1 is rep ated to prepare the hydrogel polymer with th additional step of adding 0.5 g of dodecan thiol after th allyl methacrylate is added to the mixture.

Example 6

Preparation of a Hydrogel Polymer Containing Nitroglycerin

The hydrogel polymer of this example is prepared according to the procedure of Example 1 except that 0.025 g of nitroglycerin is substituted for the pilocarpine hydrochloride.

Example 7

Preparation of a Hydrogel Polymer Containing Scopolamine

The hydrogel polymer of this example is prepared according to the procedure of Example 1 except that 0.2 g of scopolamine is substituted for the pilocarpine hydrochloride.

Claims

1. A sustained-release polymeric hydrogel dosage form useful for topical, systemic or transdermal administration of a medicinal agent comprising (1) a cross-linked, hydrophilic copolymer containing units derived from (a) an olefinically unsaturated hydrophilic monomer and (b) an amino acid monomer, and (2) a medicinal agent, wherein said medicinal agent has been incorporated by adding it to the copolymer solution obtained following initial polymerization of said monomers in a (C_1-C_4) alkyl polar solvent but prior to cross-linking of the copolymer, whereby said medicinal agent is retained in the copolymer matrix but is slowly releasable from said copolymer upon tissue contact.

2. The Sustained-release dosage form of Claim 1, wherein the olefinically unsaturated hydrophilic monomer is a hydroxyalkyl ester or amide of an alpha-,beta-unsaturated carboxylic acid or an N-vinyl lactam.

3. The sustained-release dosage form of Claim 2, wherein the olefinically unsaturated hydrophilic monomer is hydroxyethyl methacrylate.

4. The Sustained-release dosage form of any preceding claim, wherein the amino acid monomer is an alpha-,beta-unsaturated carbonyl-modified amino acid monomer.

5. The sustained-release dosage form of Claim 4, wherein the alpha-,beta-unsaturated carbonyl modifier for the amino acid monomer is an aliphatic monocarboxylic acid, an aliphatic dicarboxylic acid, an aromatic dicarboxylic acid, an aromatic tricarboxylic acid or an aromatic tetracarboxylic acid.

6. The sustained-release dosage form of Claim 5 wherein the amino acid monomer is methacroyl glycine, methacroyl glutamate, methacroyl desmosine or methacroyl isodesmosine.

7. The sustained-release dosage form of any preceding claim, wherein said copolymer is cross-linked by allyl methacrylate.

8. The sustained-release dosage form of any preceding claim, wherein said hydrophilic copolymer also contains units derived from a hydrophobic monomer.

9. The sustained-release dosage form of Claim 8, wherein a polymeric hydrogel is prepared from a polymerizable hydrophilic monomer present in the amount of 50% to 90% w/w, an amino acid monomer present in the amount of 5% to 27% w/w, a cross-linking agent present in the amount of 3% to 30% w/w and a hydrophobic monomer present in the amount of 8% to 20% w/w, the weight percentages being based on the total weight of the polymeric hydrogel.

10. The sustained-release dosage form of any preceding claim, wherein the polar solvent is an alcohol, a ketone or mixtur of keton s, a mixture of an alcohol and water in any proportion.

11. The sustain d-r leas dosag form of any preceding claim wherein said medicinal agent is an antibiotic, an antiviral, an antiinflammatory, a steroid, a peptide, a polypeptide, a cardiotonic, an

antihypertensive, an antiallergic, an alpha-adrenergic blocking agent, a beta-adrenergic blocking agent, an anticataract agent, an ophthalmic medicament, an ophthalmic lubricating agent or an ophthalmic anaesthetic agent.

12. The sustained-release dosage form of Claim 11, wherein said medicinal agent is selected from pilocarpine, idoxuridine, carbachol, bethanechol, timolol, tetracycline, epinephrine, phenylephrine, eserine, phospholine, demecarium, cyclopentolate, homatropine, scopolamine, nitroglycerin, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, penicillin, erythromycin, sulfacetamide, polymyxin B, tobramycin, isofluorophate, fluoromethalone, dexamethasone, hydrocortisone, fluorocinolone, medrysone, prednisolone, methyl prednisolone, betamethasone, triamcinolone, interferon, cromolyn, all-trans-retinoic acid and a nontoxic, pharmaceutically acceptable salt thereof.

13. The sustained-release dosage form of Claim 11, wherein said medicinal agent is an ophthalmic lubricating agent selected from polyvinyl alcohol, a cellulose polymer and a polylactam.

14. The sustained-release dosage form of any preceding claim wherein said dosage form is molded as a contact lens or ocular insert for ophthalmic administration of a systemic medicament, an ophthalmic medicament or an ophthalmic lubricating agent.

15. The sustained-release dosage form of Claim 14, wherein said contact lens has the ability to correct vision.

16. A process for the preparation of the sustained-release dosage form of any preceding claim, which comprises mixing a hydrophilic monomer, an amino acid monomer, a cross-linking agent and a lower alkyl (C_1-C_4), polar solvent and optionally a hydrophobic monomer, polymerizing at room temperature, adding a medicinal agent to the resulting linear polymer and cross-linking.

17. The process of Claim 16, wherein a catalyst and/or a chain regulator are used.

Patentansprüche

1. Polymere Hydrogelverabreichungsform mit verzögerter Wirkstoffabgabe, die für lokale, systemische oder perkutane Verabreichung eines medizinischen Mittels nützlich ist, die folgendes umfasst: (1) ein vernetztes, hydrophiles Copolymer, das Einheiten enthält, die von (a) einem olefinischen ungesättigten hydrophilen Monomer und (b) einem Aminosäurenmonomer abgeleitet sind, und (2) ein medizinisches Mittel, in dem das medizinische Mittel eingebaut worden ist, indem es der Copolymerlösung zugegeben wird, die nach der anfänglichen Polymerisation des Monomers in einem polaren (C_1-C_4)-Alkyllösungsmittel, aber vor der Vernetzung des Copolymers erhalten wurde, wobei das medizinische Mittel in der Coploymermatrix zurückgehalten wird, aber langsam von dem Copolymer abgegegeben werden kann, wenn es mit Gewebe in Kontakt kommt.

2. Verabreichungsform mit verzögerter Wirkstoffabgabe nach Anspruch 1, in der das olefinisch ungesättigte hydrophile Monomer ein Hydroxyalkylester oder Amid einer Alpha-,Beta-ungesättigten Carbonsäure oder eines N-Vinyllactams ist.

3. Verabreichungsform mit verzögerter Wirkstoffabgabe nach Anspruch 2, in der das olefinisch ungesättigte hydrophile Monomer Hydroxyethylmethacrylat ist.

4. Verabreichungsform mit verzögerter Wirkstoffabgabe nach einem der vorhergehenden Ansprüche, in der das Aminosäurenmonomer ein Alpha-,Beta-ungesättigtes, mittels Carbonyl modifiziertes Aminosäurenmonomer ist.

5. Verabreichungsform mit v rzögerter Wirkstoffabgab nach Anspruch 4, in der das Alpha-,Beta-ungesättigte Carbonylmodifikationsmittel für das Aminosäurenmonomer eine aliphatische Monocarbonsäure, eine aliphatische Dicarbonsäure, ein aromatisch Dicarbonsäure, eine aromatisch Tricarbonsäure oder eine aromatisch Tetracarbonsäure ist.

6. Verabreichungsform mit verzögerter Wirkstoffabgabe nach Anspruch 5, in der das Aminosäurenmonomer Methacroylglycin, M thacroylglutamat, Methacroyldesmosin oder Methacroylisodesmosin ist.

7. Verabreichungsform mit verzögerter Wirkstoffabgab nach einem der vorhergeh nden Ansprüch , in der das Copolymer mit Allylmethacrylat vernetzt ist.

8. Verabreichungsform mit verzögerter Wirkstoffabgabe nach einem der Vorhergehenden Ansprüche, in dar das hydrophile Copolymer auch Einheiten enthält, die von einem hydrophoben Monomer abgeleitet sind.

9. Verabreichungsform mit verzögerter Wirkstoffabgabe nach Anspruch 8, in der ein polymeres Hydrogel aus einem polymerisierbaren hydrophilen Monomer hergestellt wird, das in einer Menge von 50% bis 90% w/w vorhanden ist, einem Aminosäurenmonomer, das in einer Menge von 5% bis 27% w/w vorhanden ist, einem vernetzenden Mittel, das in einer Menge von 3% bis 30% w/w vorhanden ist und einem hydrophoben Monomer, das in einer Menge von 8% bis 20% w/w vorhanden ist, wobei die Gewichtsprozente auf dem Gesamtgewicht des polymeren Hydrogels beruhen.

10. Verabreichungsform mit verzögerter Wirkstoffabgabe nach einem der vorhergehenden Ansprüche, in der das polare Lösungsmittel ein Alkohol, ein Keton oder Mischung von Ketonen, eine Mischung eines Alkohols und Wasser in irgendeinem Verhältnis ist.

11. Verabreichungsform mit verzögerter Wirkstoffabgabe nach einem der vorhergehenden Ansprüche, in der das medizinische Mittel ein Antibiotikum, ein gegen einen Virus wirkendes Mittel, ein antientzündliches Mittel, ein Steroid, ein Peptid, ein Polypeptid, ein herzwirksames Mittel, ein gegen hohen Blutdruck wirkendes Mittel, ein antiallergenes Mittel, ein Alpha-adrenergisches Sperrmittel, ein Beta-adrenergisches Sperrmittel, ein Antikataraktmittel, ein ophthalmisches Medikament, ein ophthalmisches Schmiermittel, oder ein ophthalmisches Anästhesiemittel ist.

12. Verabreichungsform mit verzögerter Wirkstoffabgabe nach Anspruch 11, in der das medizinische Mittel von Pilocarpin, Idoxuridin, Carbachol, Bethanechol, Timolol, Tetracyclin, Epinephrin, Phenylephrin, Eserin, Phospholin, Demecarium, Cyclopentolat, Homatropin, Scopolamin, Nitroglycerin, Chlortetracyclin, Bacitracin, Neomycin, Polymyxin, Gramicidin, Oxytetracyclin, Chloramphenicol, Gentamycin, Penicillin, Erythromycin, Sulfacetamid, Polymyxin B, Tobramycin, Isofluorophat, Fluoromethalon, Dexamethason, Hydrocortison, Fluorocinolon, Medryson, Prednisolon, Methylprednisolon, Betamethason, Triamcinolon, Interferon, Cromolyn, All-transretinoischer Säure und einem nicht giftigen, pharmazeutisch annehmbaren Salz davon ausgewählt wird.

13. Verabreichungsform mit verzögerter Wirkstoffabgabe nach Anspruch 11, in der das medizinische Mittel ein ophthalmisches Schmiermittel, das von Polyvinylalkohol, einem Cellulosepolymer und einem Polylactam ausgewählt wird, ist.

14. Verabreichungsform mit verzögerter Wirkstoffabgabe nach einem der vorhergehenden Ansprüche, in der die Verabreichungsform als eine Kontaktlinse oder ein Okulareinsatz für ophthalmische Verabreichung eines systemischen Arzneimittels, eines ophthalmischen Arzneimittels oder eines ophthalmischen Schmiermittels gebildet ist.

15. Verabreichungsform mit verzögerter Wirkstoffabgabe nach Anspruch 14, in der die Kontaktlinse die Fähigkeit hat, die Sicht zu berichtigen.

16. Verfahren zur Herstellung der Verabreichungsform mit verzögerter Wirkstoffabgabe nach einem der vorhergehenden Ansprüche, das umfasst, ein hydrophiles Monomer, ein Aminosäurenmonomer, ein vernetzendes Mittel und ein polares Niedrigalkyl(C_1-C_4)-Lösungsmittel, und wahlweise ein hydrophobes Monomer zu mischen, es bei Raumtemperatur zu polymerisieren, dem sich ergebenden linearen Polymer ein medizinisches Mittel zuzugeben, und es zu vernetzen.

17. V rfahren nach Anspruch 16, in d m ein Katalysator und/oder ein Kettenregulator benutzt werden.

Revendications

1. Form d dosag à effet entret nu d'hydrogel polymèr prévue pour l'administration utile topique, systémiqu ou transdermal d'un produit médicinal comportant (1) un copolym`re hydrophile réticulé contenant des unités relevant (a) d'un monomère hydrophile oléfine non saturé et (b) d'un monomère d'aminoacide, ainsi que (2) un produit médicinal incorporé en l'ajoutant à la solution copolymère obtenue suite à la polymérisation initiale desdits monomères en solvant polaire alcoyle (C_1-C_4) mais avant la réticulation du copolymère, ledit produit médicinal étant retenu dans une matrice de copolymère mais admettant la dissipation lente depuis ledit copolymère suite au contact avec le tissu.

2. La forme de dosage à effet entretenu selon la revendication 1, suivant laquelle le monomère hydrophile oléfine non saturé d'oléfine est un amide ou ester hydroxyalcoyle d'acide carboxylique alpha , bêta ou un lactame N-vinyle.

3. La forme de dosage à effet entretenu selon la revendication 2, suivant laquelle le monomère hydrophile oléfine non saturé est le méthacrylate hydroxyéthyle.

4. La forme de dosage à effet entretenu selon l'une ou l'autre des revendications précédentes, dont le monomère d'aminoacide, suivant laquelle le monomère hydrophile d'aminoacide est un monomère aminoacide carbonyle modifié alpha, bêta non saturé.

5. La forme de dosage à effet entretenu selon la revendication 4, suivant laquelle l'agent modifiant aminoacide carbonyle alpha, bêta non saturé est un acide monocarboxyle aliphatique, un acide dicarboxyle aliphatique, un acide dicarboxyle aliphatique aromatique ou un acide tétracarboxyle aromatique.

6. La forme de dosage à effet entretenu selon la revendication 5, suivant laquelle le monomère d'aminoacide consiste de méthacroyle glycine, méthacroyle glutamate, méthacroyle desmosine ou de méthacroyle isodesmosine.

7. La forme de dosage à effet entretenu selon l'une ou l'autre des revendications précédentes, selon laquelle le copolymère est réticulé par le méthacrylate allyle.

8. La forme de dosage à effet entretenu selon l'une ou l'autre des revendications précédentes, selon laquelle le copolymère hydrophile comporte aussi des unités dérivées d'un monomère hydrophobe.

9. La forme de dosage à effet entretenu selon la revendication 8, comportant un hydrogel polymère préparé à partir de monomère hydrophyle polymérisable d'un montant de 50% à 90% par poids, un monomère amino acide d'un montant de 3% à 27% par poids, un agent réticulant d'un montant de 3% à 30% et un monomère hydrophobe d'un montant de 8% à 20% par poids, les pourcentages par poids étant basés sur le poids global d'hydrogel polymère.

10. La forme de dosage à effet entretenu selon l'une ou l'autre des revendication précédentes, dont le solvant polaire est un alcool, cétone ou mélange de cétones, un mélange d'alcool et d'eau de toutes proportions éventuelles.

11. La forme de dosage à effet entretenu selon l'une ou l'autre des revendication précédentes, suivant laquelle ledit produit médicinal est un agent antibiotique, antiviral, antiinflammatoire, stéroïde, peptide, polypeptide, cardiotonique, anti-hypertensif, antiallergique, un agent bloqueur alpha-adrénergique, un agent bloqueur bêta-adrénergique, un agent anti-cataracte, un médicament ophtalmique, un agent lubrifiant ophtalmique ou un agent anesthésique ophtalmique.

12. La forme de dosage à effet entretenu selon la revendication 11, dont l'agent médicinal est sélectionné à partir de pilocarpine, idoxuridine, carbachol, béthanéchol, timoloi, tétracyclin , épinéphrine, ph nylephrine, éserine, phospholine, dém carium, cyclopentolate, homatropine, scopolamine, nitroglycérin , chlortétracycline, bacitracin , néomycine, polymyxine, gramicidine, oxitétracycline, chloramphénicol, gentamycine, pénicilline, erythromycine, sulphacétamide, polymyxine B, tobramycin , isofluorophate, fluorométhalone, dexaméthasone, hydrocortisone, fluorocinolone, médrysone, prednisolone, méthyle

prednisolon , bétaméthasone, triamcinolone, interféron, cromolyne, tout acide trans-rétinoïqu et un s l non-toxique conn x d class pharmaceutique admissibl .

13. La forme de dosag à effet entr t nu selon la revendication 11, dont ledit agent médicinal est un agent ophtalmique lubrifiant sélectionné à partir d'alcool polyvinyle, de polymère de cellulose et de polylactame.

14. La forme de dosage à effet entretenu selon l'une ou l'autre des revendications précédentes, suivant laquelle ladite forme de dosage est moulée sous forme de lentille de contact ou d'insert oculaire pour l'administration ophtalmique d'un mèdicament systémique, un médicament ophtalmique ou un agent lubrifiant ophtalmique.

15. La forme de dosage à effet entretenu selon la revendication 14, dont ladite lentille de contact est en mesure de corriger la vue.

16. Le procédé de préparation de forme de dosage à effet entretenu selon l'une ou l'autre des revendications précédentes, comportant un monomère hydrophile, un monomère aminoacide, un agent réticulant et un alcoyle inférieur (C_1-C_4), du solvant polaire et en option un monomère hydrophobe, la polymérisation à température ambiante, l'apport d'un agent médicinal au polymère linéaire qui en résulte et la réticulation.

17. Le procédé selon la revendication 16, suivant laquelle un catalyseur et/ou un régulateur de chaîne sont exploités.

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